Iranian Journal of Veterinary Science and Technology
Vol. 3, No. 2, 2011, 41-48

IJVST

Enhancing analgesic effects of lidocaine in rabbit epidural analgesia using metoclopramide or tramadol

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Received: October 2, 2011 Accepted: January 22, 2012

Abstract

The objective of the present experience was to study the effects of metoclopramide and tramadol on epidural analgesia induced by lidocaine in rabbits.Fifteen healthy New Zealand White rabbits weighting 3-3.5 kg of both genders were used.Animals were divided randomly into three groups. Three different combinations of drugs were injected into the epidural space to induce epidural analgesia in the following order: group A2% lidocaine (1.5 ml), group B the combination of 2% lidocaine (1.5 ml) and metoclopramide (0.5 ml) and group C, the combination of 2% lidocaine (1.5 ml) and tramadol (0.2 ml). The procedure was repeated 48 hours and a week after the first injection. The onset time of analgesia (OT), duration of flaccid paresis (DFP) and duration of analgesia (DA) was determined in all treatments. There was no complication in the induction of epidural analgesia.Statistical analysis showed thatmean of OT in group C (15.7±4.2 sec), was significantly lower in comparison to group A (68.6±15.5 sec) and group B (45.8±17.1 sec)(p=0.004). Mean DFP was significantly higher in group C (35.9±10.5 min) in comparison to group A (18.3±5.2 min) and group B (29.2±11.5 min)(p = 0.001). Mean of DA was significantly higher in group B (39.1±16.2 min) compared to group A (23.6±5.5 min)(p=0.018) and also in group C (48.9±10.7 min) compared to group A (p =0.00). But there was no significant difference between means of DA in group B and C (p =0.05).The present study indicates that addition ofmetoclopramide and tramadol to lidocaine is effective in prolongation of epidural analgesia in rabbit.

Keywords: epidural analgesia, lidocaine, metoclopramide,tramadol, rabbit

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Introduction

Epidural analgesia, a form of regional anesthesia, is an effective route to produce loss of pain and sensation by injecting drugs into the epidural space.It is probably the most useful method to control post-operative pain after an abdominal surgery (Gürses *et al.,* 2003). After lidocaine was introduced in veterinary practice in 1944, it became a popular drug to induce epidural analgesia.Since then a variety of drugs and their combinations have been reported in human and veterinary literature to induce epidural analgesia alone or adjunct to other methods of anesthesia for abdominal and perinealsurgeries, obstetric manipulations andcesarean section, tail amputation and rear limb surgeries. It is also used to produce post-operative analgesia and relieve pain in patients with chronic pain. In spite of described advantages of epidural analgesia, it is not widely used in small animal practice. This may be due to the fact that some surgeons are not fully familiar with the technique or they prefer one venous puncture to induce analgesia (Hall and Clarke, 2001, Johnston, 2005).

Administration of opioids is one of the most common techniques to produce epidural analgesia (Gürses *et al.,* 2003).A central acting synthesized opioid called tramadol HCl, is widely used for the management of moderate to moderately severe pain and for long-term treatment of chronic pain in continuous epidural block keep. Like other opioids, it is also used to produce preemptive and post-operative analgesia in epidural route as well (Gürses *et al.,* 2003, Hall and Clarke, 2001).In clinical studies, successful epidural analgesia by administration of other non-opioid drugs like ketamine, deroperidol, clonidine, xylazine and metoclopramide have been stated (Gürses *et al.,* 2003, Armand *et al.,* 1998, Tsai *et al.,* 2001, Olschewski *et al.,* 2000). There are many reports describing analgesic effects of metoclopramide, a potent dopamine receptor antagonist, that is primarily used to treat nausea and vomiting. Significant analgesic properties of metoclopramide have been demonstrateded by many authors since 1986 (Ramaswamy and Bapna, 1986). Also its analgesic effects have been described in specific surgeries like prosthetic hip surgery and knee arthroscopy (Ramaswamy and Bapna, 1986, Lisander and Kandler, 1993, Lisander, 1993, Rosenblatt *et al.,* 1991, Cicek *et al.,* 2004). Derbent in 2005 showed that pre-operative administration of metoclopramide provided post-operative analgesia in patients undergoing elective laminectomy (Derbent *et al.,* 2005).

Although some hypotheses are existed for analgesic properties of metoclopramide, its mechanism of action has not been determined yet (Kurtipek *et al.,* 1999, Hedenbro and Olsson, 1988). At present, there is no ideal drug or combination of drugs for postoperative epidural analgesia (Gürses *et al.,* 2003).

Since limitations exist for prescribing opioids; use of other analgesic drugs seems valuable. Therefore the present experimental animal modeling was conducted to study effects of metoclopramide and tramadol on epidural analgesia induced by lidocaine in rabbits.

Materials and methods

Fifteen adult and healthy New Zealand White rabbits weighting 3-3.5 kg of both genders randomly were divided into three groups. All experimental procedures were performed after approval received by the University Research Committee in accordance with the guidelines of its Institutional Animal Experimentation Ethics Committee. After aseptic preparation epidural injection was performed thorough the deepest area felt in lumbosacral (L-S) junction via a 50 mm, 20 gauge epidural needle. The hind legs of the rabbits were flexed to allow maximal opening of the lumbosacral space. The procedure for lumbosacral epidural puncture in rabbits is similar to the described procedure in literature for dogs and cats (Gaynor and Mama, 2002). Hanging drop technique was used to realize

that the needle is located into the epidural space. However before starting the project, the exact site of epidural injection was observed in a cadaver. In group A, 1.5 ml lidocaine (2%, Iran-Teb) was used to induce epidural analgesia. In group B the combination of 1.5 ml lidocaineand 0.5 ml metoclopramide HCl (0.5%, Tehran-Chimie)and in group C, the combination of1.5 mllidocaineand 0.2 ml tramadol (5%, Tehran-Chimie) was used to induce epidural analgesia. The same procedure was performed 48 hours and a week later in all rabbits. The onset time of analgesia (OT)(time measured between injection of the drug and dropping down of the tail), duration of flaccid paresis (DFP) (time measured between injection of drug and starting to walk in rabbits)and duration of analgesia (DA) (time measured between injection of the drug and returning sense of pain in tail and both hind limbs) were measured in all treatments in group A, B and C. One week after the last injection microscopic sections were obtained from all spinal cords of the subjects to study the possibility of histological changes of the tissues from 2 cm proximal and distal of the sites of injection.

Mean of the measured variables were compared among groups and between injections using between-groups and within-groups (repeated measure) analysis of variances (ANOVA). Then Banferroni test was performed for pair wise comparison between means. The p values less than 0.05 were considered statistically significant.

Results

The results are illustrated in table 1. Statistical analysis indicated that there was not a significant difference among means of OT, DFP and DA in first, second and third injection ($p>0.05$).

The results showed that there were significant differencesbetween means of OT ($p=0.004$) in group A (68.6±15.5 sec) and B(45.8±17.1 sec)versus C (15.7± 4.2 sec) which was significantly shorter. The latency of onset of analgesia was not changed by adding metoclopramide to lidocaine.

There was a significant difference between means of DFP ($p=0.001$) and means of DA ($p=0.00$) among groups. Mean of DFP was significantly longer in group C (35.9±10.5 min) ($p<0.05$) in comparison to group A (18.3±5.2 min) and group B (29.2±11.5).Mean of DA was significantly longer ($p=0.018$) in group B (39.1±16.2 min) compared to group A (23.6±5.5 min). Also mean of DA was significantly longer ($p=0.00$) in group C (48.9± 10.7 min) compared to group A. No complication occurred during induction of epidural analgesia in the rabbits. Microscopic evaluations revealed no pathologic changes, atrophy or signs of inflammation following the injections in all groups (Fig. 1).

Table 1. Mean and standard deviation of the measured variables after administration of drugs to induce epidural analgesia.

	Group A 2% Lidocaine	**Group B** Combination of 2% lidocaine and metoclopramide	**Group C** Combination of 2% lidocaine and tramadol
Onset time (sec)	68.6±15.5^{a}	45.8±17.1^{a}	15.7±4.2*
Duration of flaccid paresis (min)	18.3±5.2^{b}	29.2±11.5^{b}	35.9±10.5*
Duration of analgesia (min)	23.6±5.5*	39.1±16.2^{c}	48.9±10.7^{c}

The measured variables in groups with the common superscripts were not significantly different from each other at the 0.05 significance level.
* Significantly different from other groups.

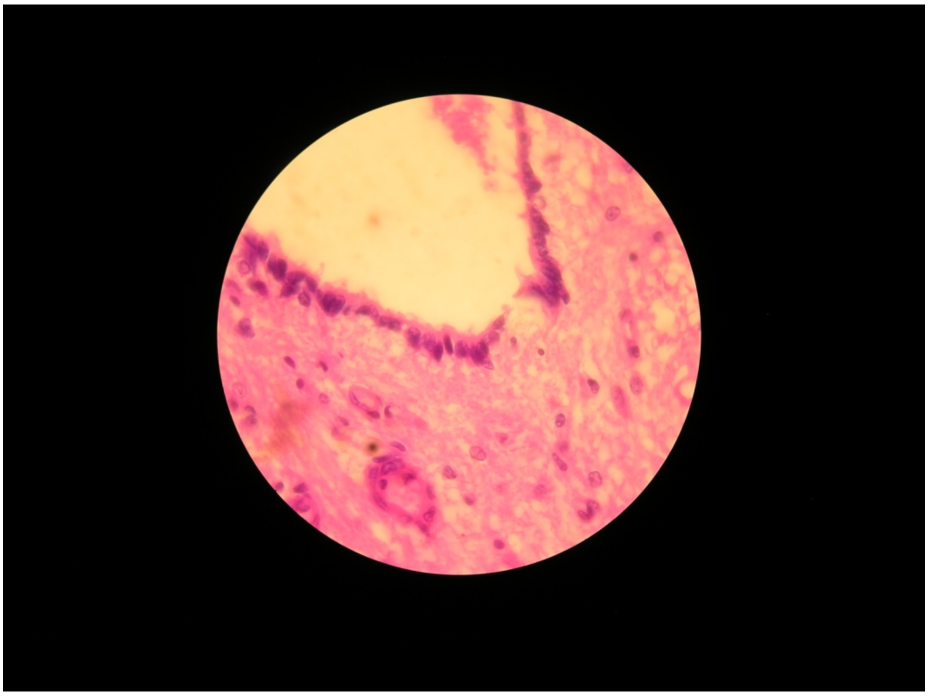


Figure. 1. Cross section of the spinal cord. Normal columnrt ependymal cells covering the inner surface of the central canal are observed. Hematoxylin and eosin, ×100.

Discussion

Epidural analgesia can be performed in several surgical and painful procedures in addition of the ability to produce post-operative analgesia and continuous pain relief in patients with chronic pain such as patients with advanced stage of cancers, intervertebral disk or neurologic problems. Rabbit was used in the present experiment because reports showed that rabbit is a suitable model for inducing epidural block and evaluating sensory and motor loss under standardized experimental conditions (Johnston, 2005, Malinovsky *et al.*, 1997). The procedure for lumbosacral epidural puncture in ferrets and rabbits is similar to that described in literature for dogs and cats, except that there is rarely a definitive popping sensation when the intervertebral ligaments are punctured at the time of entry into the epidural space (Gaynor and Mamma, 2002). We did not encounter a problem during performing epidural analgesia, because the method was examined in pilot models and the injection site was carefully detected in cadaver.

Mean onset time of analgesia was significantly shorter when the combination of tramadol and 2% lidocaine was used in group C (p=0.004). Although mean onset time of analgesia was longerin the combination of metoclopramide and 2% lidocainein group B (45.8±17.1sec) it was not significantly different from the one of 2% lidocainethat used alone (p>0.05). This indicates that tramadol speeds up the onset time of analgesia, but metoclopramide does not have the ability of shortening the onset time of analgesia in epidural injection. Previous report by Komoda indicated that the addition of deoxyaconitine, a traditional drug used to alleviate pain which is an opioid agonist, to lidocaine in epidural analgesia does not change the latency of onset time of analgesia in rabbits (Komoda *et al.*, 2003). But our findings indicate that tramadol, an opioid drug, can speed up the onset time of analgesia, but metoclopramide does not have the ability of lowering the onset time of analgesia in epidural injection. Our findings were not in agreement with their results.

Duration of flaccid paresis was significantly longer in group C in comparison to group A and B ($p<0.05$), in spite of higher mean of DFP when combination of metoclopramide and 2%lidocaine was used (Table. 1). This indicated that metoclopramide may have less or even no motor block properties versus tramadol. A synergism was reported in the epidural space between lidocaine and opioids, and their combination can decrease side effects of each individual drug (Hall and Clarke, 2001, Wang *et al.,* 1993). However the risk of respiratory depression increases with repeated and continuous administration of epidural opioids, tramadol may be advantageous because of a low risk of respiratory depression (Delikan and Vijayan, 1993, Baraka *et al.,* 1993). There are reports of other combinations with lidocaine that can improve its motor block activities. Doherty *et al.* reported that ionic complexes of local anesthetics such aslidocaine with medium molecular weight hyaluronic acid formulations can prolong loss of weight bearing twofold in local anesthesia in rabbit (Dohert *et al.,* 1995). Komoda *et al.* reported 60% extension of duration of flaccid paresis by addition of deoxaconitine to lidocaine in comparison to lidocaine alone (Komoda *et al.,* 2003).

Means of duration of analgesia were significantly increased whether metoclopramide (p=0.018) or tramadol (p=0.00) was added to 2% lidocaine. There was no significant difference between prolongation of analgesia when tramadol or metoclopramide was added to 2% lidocaine ($p>0.05$).This highlightsanalgesic effects of metoclopramide as previously illustrated. Although the analgesic properties of the popular anti-emetic, metoclopramide, have been demonstrated since several years ago, it's mechanism of action is still controversial (Ramaswamy and Bapna, 1986, Cicek *et al.,* 2004). There are some reports that show its analgesic effect was reduced by naloxone suggesting an opioid involvement of metoclopramide (Ramaswamy and Bapna, 1986). However it did not alter the antinociceptive effects of morphine. This suggests a lack of interaction between opioids and metoclopramide (Ung *et al.,* 2008). Also there are reports of a relationship between serum levels of prolactin and analgesia produced by metoclopramide (Lisander, 1993, Kurtipek*et al.,* 1999). In 1992 Ganta *et al.,* reported the equal analgesic effects of lidocaine and metoclopramide in prevention of pain caused by the injection of propofol (Ganta and Fee, 1992). No pathologic changes were reported during repetitive epidural injection of metoclopramide in rabbits by Kurtipek in 1999. This finding is consistent with the findings of the present study (Kutripek *et al.,* 1999)**.** Since no significant damage was observed in microscopic evaluations of the spinal cords, the drugs can be used safe to induce epidural analgesia.

It is concluded that the addition of tramadol to lidocaine in epidural analgesia induced in rabbit not only speeds up the onset time of analgesia, but also prolongs the duration of flaccid paresis and analgesia. Metoclopramide, a frequently antiemetic prescribed, can extend the duration of epidural analgesia induced by lidociane in comparison to lidocaine alone. Nevertheless no evidence was found to indicate whether its addition to lidocaine can also prolong the duration of flaccid paresis.

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Iranian Journal of Veterinary Science and Technology
Vol. 3, No. 2, 2011, 41-48

IJVST

افزودن اثرات بی‌حس کنندگی اپیدورال لیدوکایین در خرگوش بوسیله متوکلوپرامید یا ترامادول

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دریافت مقاله: ۱۳۹۰/۷/۱۰　　*پذیرش نهایی: ۱۳۹۰/۱۱/۲*

چکیده

در این مطالعه اثرات افزودن متوکلوپرامید و ترامادول به لیدوکایین در بی حسی اپیدورال در خرگوش مورد بررسی قرار گرفت. پانزده خرگوش نیوزیلندی سفید با متوسط وزنی ۳/۵-۳ کیلوگرم از هر دو جنس نر و ماده انتخاب شد. حیوانات به طور تصادفی به سه گروه تقسیم شدند. سه ترکیب دارویی مختلف به داخل فضای اپیدورال جهت انجام بی حسی اپیدورال تزریق شد. در گروه A لیدوکایین ۲ درصد (۱/۵ سی سی)، در گروهB ترکیب لیدوکایین ۲ درصد (۱/۵ سی سی) و متوکلوپرامید (۰/۵ سی سی) و در گروه C ترکیب لیدوکایین ۲ درصد (۱/۵ سی سی) و ترامادول (۰/۲ سی سی) تزریق شد. این عمل ۴۸ ساعت و یک هفته بعد از اولین تزریق مجددا تکرار شد. شروع بی‌حسی، متوسط فلجی و شلی اندام حرکتی خلفی و طول مدت بی دردی در تمامی گروه ها مورد ارزیابی قرار گرفت. بعد از تزریق داروی بی‌حسی به داخل فضای اپیدورال هیچ عارضه ی جانبی دیده نشد. مطالعات آماری نشان داد که شروع اثر بی دردی در گروه C (۴/۲ ± ۱۵/۷ ثانیه) به‌طور معنی داری کم تر از گروهA (۱۵/۵ ± ۶۸/۶ثانیه) و گروه B (۱۷/۱±۴۵/۸ ثانیه) بود (p=0.004). فلجی و شلی اندام حرکتی خلفی به طور قابل ملاحظه‌ای در گروه C (۱۰/۵± ۳۵/۹ دقیقه) بالاتر از گروه A (۵/۲ ± ۱۸/۳ دقیقه) و گروه B (۱۱/۵ ± ۲۹/۲ دقیقه) بود (p= 0.001). متوسط طول مدت بی دردی در گروه B (۱۶/۲ ± ۳۹/۱ دقیقه) به طور معنی داری بیشتر از گروه A (۵/۵ ± ۲۳/۶ دقیقه) (p=0.018) و همچنین در گروه C (۱۰/۷±۴۸/۹ دقیقه) در مقایسه با گروه A بود (p=0.00). هیچ اختلاف معنی داری از نظر طول مدت بی‌دردی بین گروه B و C دیده نشد. افزودن متوکلوپرامید و ترامادول به لیدوکایین در بی حسی اپیدورال باعث افزایش طول مدت بی‌دردی در خرگوش‌ها می شود.

واژگان کلیدی: بی حسی اپیدورال، لیدوکایین، متوکلوپرامید، ترامادول، خرگوش